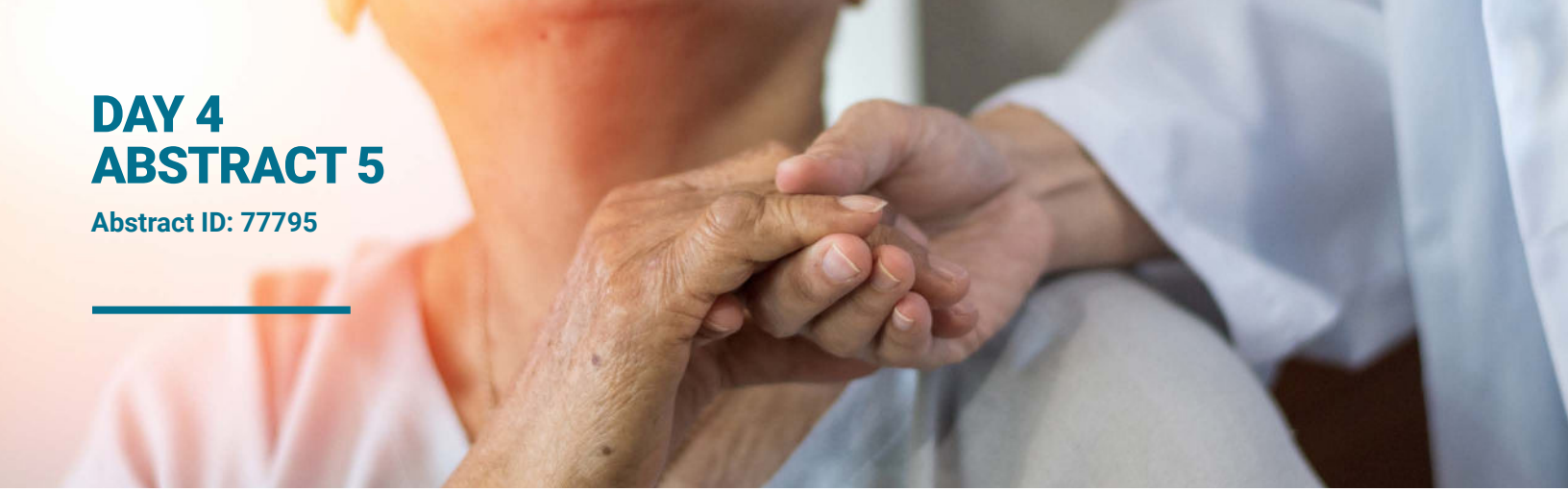

DAY 4
ABSTRACT 5

Abstract ID: 77795

Implications of ARIA for trial design and monitoring

Abstract: **Frank J. Wolters, MD, PhD**, Department of Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands

Background: Side-effects of therapy with monoclonal antibodies against Alzheimer's disease are common, which has important consequences for treatment monitoring. Moreover, adverse effects may affect trial validity through unblinding of participants, but impact on trial results is uncertain.

Method: Literature review, and simulation modelling using observations from published randomised placebo-controlled clinical trials (RCTs) of monoclonal antibodies against amyloid-β.

Result: In analysis of simulated trial data, we demonstrate the impact of disclosure of treatment status on cognitive and functional endpoints in RCTs. These analyses show the likelihood that placebo effects after unblinding contribute to the observed treatment effects. We define the most prudent targets for safeguarding causal inference from RCTs, and suggest mitigation strategies for future trial conduct. Furthermore, we consider best practice for treatment selection and monitoring in light of amyloid-related imaging abnormalities (ARIA). Specifically, we discuss i) the implications of interaction with other, concurrently used medication (e.g. antithrombotic drugs) on treatment safety, and ii) challenges in treatment monitoring on the basis of observed rates of ARIA with monoclonal antibody treatment, as well as background risk of hemorrhagic ARIA in the general population and in placebo-groups of published RCTs. We end with recommendations for future research on the most pressing ARIA-related questions for implementation of monoclonal antibodies in routine practice.

Conclusion: Simulated trial data can offer valuable insight in the interpretation and design of RCTs against Alzheimer's disease. Better understanding of ARIA in different patient groups is needed to guide treatment indication and monitoring.